DESIGN AND OPTIMIZATION OF ORODISSOLVING TABLET OF ANTIDEPRESSANT DRUG BY SUPERDISINTEGRANTS ADDITION METHOD

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ABSTRACT

The purpose of this research was to develop mouth dissolving tablet of fluoxetine. Mouth dissolving tablet offers a solution for pediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. Fluoxetine have become first line drug in the pharmacotherapy of patients with depression. This is because the drug possesses tolerability and safety advantages over the tricyclic agents. The aim is to formulate fifteen formulations of fast dissolving tablet of fluoxetine using different superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone and Pregelatinized starch) by wet granulation method. The tablets were evaluated for hardness, thickness, friability, weight variation, uniformity of content, disintegration time and dissolution studies. *In vitro* dissolution studies show the release is in the following order of superdisintegrants: **Crospovidone > Pregelatinized starch > Croscarmellose > Sodium Starch Glycolate**. Maximum *in vitro* dissolution was found to be with formulation F-7 and it clearly shows due to crospovidone (4%), this is also confirmed by *In vivo* pharmacokinetic studies. From the above data's it has been found and concluded, crospovidone at a concentration of 4% w/w is suitable for preparing oro-dissolving tablet of fluoxetine.

Keywords: Fluoxetine, orodissolving tablets, super disintegrants, antidepressants

INTRODUCTION

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however hand tremors, dysphasia in case of geriatric patients, the underdeveloped muscular and nervous systems in young individuals and incase of uncooperative patients, the problem of swallowing is common phenomenon which leads to poor patient compliance.

To overcome these drawbacks, mouth dissolving tablets (MDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds'. According to European Pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes. The basic approach used in development of MDT is the use of superdisintegrants like Cross linked carboxy methylcellulose (Croscarmeliose), Sodium starch glycolate (Primogel), Polyvinyl pyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subject to first pass metabolism is reduced as compared to standard tablets.

The need for delivering drugs to patients efficiently and with few side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. A solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as fast dissolving dosage form or mouth dissolving tablets [1]. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. They are also known as oro-dissolving, rapid –dissolve oro-dispersible, melt in mouth, rapimelt, quick dissolving, fast melts, and porous tablets.

For treatment of depression various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but the major drawbacks with these are many patients find it difficult to swallow (dysphagia) tablets and hard gelatin capsules. The difficulty experienced in particular by pediatrics and geriatrics patients [2]. Other groups that may experience problems include the mentally ill, developmentally disable and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient non-compliance.

Fluoxetine have become first line drug in the pharmacotherapy of patients with depression. This is because the drug possesses tolerability and safety advantages over the tricyclic agents [3]. The concept of formulating orodissolving tablets containing fluoxetine offers a suitable and practical approach in serving desired objective of rapid disintegration and dissolution characteristics with increased bioavailability. Hence the aim is to formulate oro- dissolving tablet of fluoxetine, using various superdisintegrants and to choose a best formulation and to carry out *in vivo* bioavailability studies.

MATERIALS

Crospovidone, Croscarmellose, Fluoxetine (Paxmy Speciality Chemicals, Chennai) Pregelatinized starch (Colorcon Ltd., Goa), Sodium starch glycolate – Type A (SD Fine Chemicals Ltd., Mumbai).

METHOD

Nine formulations were prepared by wet granulation method [4] using different superdisintegrants such as Sodium Starch Glycolate, Croscarmellose, Crospovidone and Pregelatinized starch in various ratios (designated as F-2, F-3, F-4, F-5, F-6, F-7 F-8 and F-9) and formulation F-1 prepared without superdisintegrant is used as control (Table 1).

Wet granulation method using superdisintegrants

Fluoxetine raw material and all excipients were passed through sieve no.60 before granulation and lubrication. The required quantity of Fluoxetine and other excipients (except lubricants and glidants) were weighed and mixed uniformly. Then the mixture was made to a damp mass using starch paste. Then the prepared mass was passed through sieve no. 16. The prepared granules were dried in an oven at a temperature of 50°C for one hour. The granules obtained were lubricated by adding and mixing with talc, magnesium stearate and colloidal silicon dioxide. The lubricated granules were evaluated and punched into tablets with an average weight of 200 mg, using Cadmach tabletting machine.

Raw material evaluation of fluoxetine hydrochloride drug

Identification: By Infrared Absorption spectroscopy (Figure 1).

Evaluation of lubricated granules

The lubricated granules prepared were evaluated [4] for the following official parameters such as bulk density, tapped density, Carr's index, Hausners ratio and angle of repose as per official procedures. The values of all the evaluation parameters are summarized in (Table 2)

Table 1: The formula for Fluoxetine Hydrochloride orodissolving Tablet

Ingredients	Quantity per tablet (mg)								
Sodium starch glycolate	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
	-	4	8	-	-	-	-	-	-
Croscarmellose	-	-	-	4	8	-	-	-	-
Crospovidone	-	-	-	-	-	4	8	-	-
Pregelatinized starch	-	-	-	-	-	-	-	4	8
Fluoxetine	10								
Microcrystalline cellulose	60								
Saccharin sodium	1								
Starch paste	10								
Magnesium stearate	2								
Talc	1								
Colloidal silicon dioxide	1								
Mannitol up to…	**200**								

Table 2: Evaluation of lubricated granules of fluoxetine orodissolving tablet

S. No	Formulations	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Angle of repose (º)	Hausner's ratio
1	F-1	0.392	0.399	18.03	28º 37'	1.018
2	F-2	0.361	0.408	11.59	28º 07'	1.131
3	F-3	0.387	0.434	10.86	29º 37'	1.121
4	F-4	0.414	0.462	10.31	27º 21'	1.115
5	F-5	0.372	0.421	11.52	27º 21'	1.130
6	F-6	0.359	0.421	14.62	28º 22'	1.170
7	F-7	0.375	0.414	9.42	27º 28'	1.104
8	F-8	0.366	0.411	10.90	27º 18'	1.122
9	F-9	0.376	0.442	15.08	28º 22'	1.177

Table 3: Evaluation of fluoxetine orodissolving tablet

Formulations	Weight Variation	Thickness (mm) ± S.D	Hardness (Kg/cm^2)	Friability (% w/w) Mean ± S.D	Drug content ± S.D	Wetting time (secs) ± S.D	In-vitro disintegration time (secs) ± S.D
F-1	Pass	5.22 ± 0.01	4 - 4.5	0.49 ± 0.04	9.57 ± 0.06	92 ± 0.74	90 ±1.73
F-2	Pass	5.20 ± 0.03	3.5- 4	0.65 ± 0.07	9.94 ± 0.07	41 ± 2.13	40 ±2.86
F-3	Pass	5.18 ± 0.02	4	0.82 ± 0.02	9.88 ± 0.24	38 ± 1.89	36 ± 1.0
F-4	Pass	5.20 ± 0.01	3.5 - 4	0.30 ± 0.01	9.97 ± 0.19	35 ±1.65	33 ± 0.42
F-5	Pass	5.19 ± 0.02	4	0.54 ± 0.05	9.98 ± 0.12	71 ± 1.04	70 ± 2.16
F-6	Pass	5.21 ± 0.02	3.5 - 4	0.79 ± 0.04	9.97 ± 0.20	43 ± 0.88	41 ± 2.54
F-7	Pass	5.19 ± 0.03	3.5 - 4	0.66 ± 0.04	10.03 ± 0.07	11 ± 1.56	10 ± 2.65
F-8	Pass	5.14 ± 0.01	3.5	0.59 ± 0.08	9.63 ± 0.21	83 ± 1.04	81 ± 2.56
F-9	Pass	5.19 ± 0.01	3.5- 4	0.40 ± 0.02	10.09 ± 0.00	42 ± 0.89	40 ± 0.06

All the values are expressed as mean ± SD

Table 4: Comparison of percentage drug release of fluoxetine orodissolving tablet

S. No	Formulations	Superdisintegrants	Ratio (% w/w)	*In vitro* drug release in 60 minutes (%)
1	F-1	Control	-	73.85
2	F-2	Sodium Starch Glycolate	2%	78.38
3	F-3		4%	83.07
4	F-4	Croscarmellose	2%	86.63
5	F-5		4%	89.17
6	F-6	Crospovidone	2%	90.16
7	F-7		4%	96.94
8	F-8	Pregelatinized starch	2%	88.90
9	F-9		4%	91.12

Table 5: Release kinetics analysis of fluoxetine orodissolving tablet

S. No	Time (minutes)	Zero order Cumulative drug release (mg) (Q_t)	First order Log % of drug release {Log (Q_0-Q_t)}
1.	5	6.479	0.547
2.	10	7.145	0.456
3.	15	7.851	0.332
4.	20	9.445	-0.255
5.	30	9.474	-0.279
6.	45	9.483	-0.287
7.	60	9.483	-0.287

Evaluation of tablets

All the compressed tablets were evaluated [5] for the following parameters. The results were shown in (Table 3)

Thickness: The thickness of the tablets was measured by using digital vernier callipers. [5].

Uniformity of weight: 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not [5].

Hardness: Hardness of the tablet was determined using the Monsanto hardness tester [5].

Friability test: Tablets equivalent to 6.5g were placed in the apparatus, which was given 100 revolutions and the tablets were reweighed [5].

Percentage friability =

$$\frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Drug content: 20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 10 mg of fluoxetine was transferred into a 100 ml standard flask and volume was made up with 0.1N hydrochloric acid. Further 1ml of the above solution was diluted to 10 ml with 0.1N hydrochloric acid and absorbance of the resulting solution was observed at 225nm [5].

Wetting time: A piece of tissue paper folded double was placed in a Petri dish containing 6ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0 C. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue [5].

Disintegration test: Fast dissolving tablets should disintegrate within 3 mts. 6 tablets of each formulation were taken and placed in 6 tubes of disintegration apparatus. The time taken for complete disintegration was noted [5].

***In- vitro* dissolution studies:**

The dissolution test [6] has been carried out for all the formulations. The in vitro drug release is performed using USP dissolution apparatus- II, 24 type paddle apparatus using 900 ml of 0.1 N HCL at paddle rotation of 50 rpm at 37±0.5ºC. 5 ml of the samples were withdrawn at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60 mins for a period of 60 mins and replaced with the fresh medium of 0.1 N HCL. The samples were filtered through 0.45 mm membrane filter, suitably diluted and analyzed at 225 nm using double beam UV/Visible spectrophotometer (Shimadzu Corporation, UV-1601, Japan). The content of drug was calculated using equation generated from standard calibration curve. The results were shown in (Table 4) and (Figure 5)

EVALUATION OF BEST FORMULATION

The formulation exhibiting faster disintegration, better *in vitro* dissolution profile and other optimum properties was considered as best among the other formulations and were subjected to the following tests,

Infra-red study: The drug and drug-excipient mixture of formulation F-7 were subjected to Infra-red (IR) studies [7] to check drug-excipient interaction. (Figure 1& 2)

Differential scanning calorimetric (DSC) study: The pure fluoxetine drug and formulation F-7 were subjected to differential scanning calorimetric study [8] performed on a NETZSCH DSC 204 instrument to asses drug- excipient compatibility. (Figure 3 & 4)

Release kinetics: The *in vitro* release data of F-7 was fitted in the kinetic equations [9] to find out the mechanism of fluoxetine release from the fast dissolving tablet. The kinetic models used were zero order and first order equation. Correlation coefficient was determined for both the equations. The results were shown in (Table 5) & (Figure 6 & 7).

In vivo release study of fluoxetine fast dissolving tablet

Formulation F- 7 (test) and F-1 (control) were subjected to *in vivo* release studies [10, 11] using rabbit as animal model. Six male rabbits weighing 1.5 kg and 12 months old were selected for the study. They were divided into two groups of 3 in each and the study was conducted as single dose randomized parallel design. The animals were housed individually under (23 ± 2 ^{o}C, 55 ± 5 % RH, 12 hours light/dark cycle) environmental conditions. The rabbits were fasted overnight and allowed free access to tap water only.

The test formulation F-7 and control formulation F-1 were administered to the rabbits by gastric intubation method after calculating the animal dose[70]. 1 ml of blood samples were withdrawn from the marginal ear vein of rabbit at 0.25, 0.50, 0.75, 1, 2, 3,4 and 6 hrs. The plasma samples were separated by centrifugation and the drug was extracted. Then the samples were assayed by high performance liquid chromatography. The results were shown in (Table 6) and (Figure 8)

Stability studies of fluoxetine orodissolving tablet

Formulation F-7 was stored in stability chamber at 45^{o}C ± 2^{o}C temperature and 75 % ± 5% relative humidity. Samples of tablets were analyzed at initial, 15th day and 45th day for physical characters and assay was performed followed by disintegration and *in vitro* dissolution test [12]. The results were shown in (Table 7).

RESULTS AND DISCUSSION

The lubricated granules parameters were satisfactory and showed good flowability. With this the granules were found to be free flowing material and showed suitability to be compressed as tablets of expected weight.

Thickness ranged from 5.14 – 5.22. Uniformity of weight was observed to be within the I.P. limits. Hardness was observed to be within the limit in the range of 3.5 – 4.0 except for control formulation the hardness was found to be 4.5 kg/cm^2. Friability was observed between percent 0.30 – 0.82 % w/w hence within the limit of > 1%. The results of drug content for all formulations were found to be between 95 % – 101.0 % hence within the IP limit of 85.0 % - 115.0 %.

Disintegration time was found to be between 10 -90 seconds. The recommended limit for fast dissolving tablets is that it should disintegrate within 3 minutes. Therefore, all formulations are within this limit and pass the test. The disintegration time (D.T) is higher for control (90 secs) and F-7 shows fast disintegration time of 10 seconds. Wetting time, is an important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water were found to be in the range of 11-92 secs respectively.

In vitro dissolution test reveals the release increases from 73% to a maximum of almost 97%. The release is in the following order of superdisintegrants: Crospovidone > Pregelatinized starch > Croscarmellose > Sodium Starch Glycolate. The maximum *in vitro* dissolution was found to be with formulation F-7. The control formulation has the least *in vitro* dissolution (73.85 %) and the formulation F-

7 was found to contain maximum in vitro dissolution of 96.97%. It clearly shows due to the superdisintegrant – crospovidone (5%) and it seems to be the best. The reason is its highly porous structure and water wicking mechanism into porous network of tablet and hence increases in concentration of crospovidone accounts for rapid drug release.

Table 6: *In- vivo* release study of control (F-1) and test (F-7) formulation in rabbits

S. No	Sampling time (Hrs)	Control (F-1) Plasma concentration (µg/ml) (Mean ± S.D)	Test (F-7) Plasma concentration (µg/ml) (Mean ± S.D)
1.	0	0.00	0.00
2.	0.25	3.12±0.06	9.13±0.06
3.	0.50	8.7±0.11	20.62±0.12
4.	0.75	14.21±0.12	24.81±0.07
5.	1	18.11±0.09	26.01±0.06
6.	2	17.56±0.03	23.14±0.03
7.	3	15.91±0.05	22±0.09
8.	4	15.5±0.08	19.84±0.06
9.	6	12.41±0.07	16.66±0.04

Table 7: Accelerated Stability Studies of formulation F-7

S. No	Temperature (°C)	Relative Humidity (%)	Time (Days)	Thickness (mm)	Hardness (Kg/cm^2)	Drug Content (%)	Disintegration Time (Secs)	Drug release (%)
1	45±2	75±5	0	5.22	3.94	97.72	10	96.94
2	45±2	75±5	15	5.22	3.95	97.70	12	96.35
3	45±2	75±5	45	5.23	3.92	97.64	12	95.4

Figure 1: IR Spectroscopy of Fluoxetine Hydrochloride

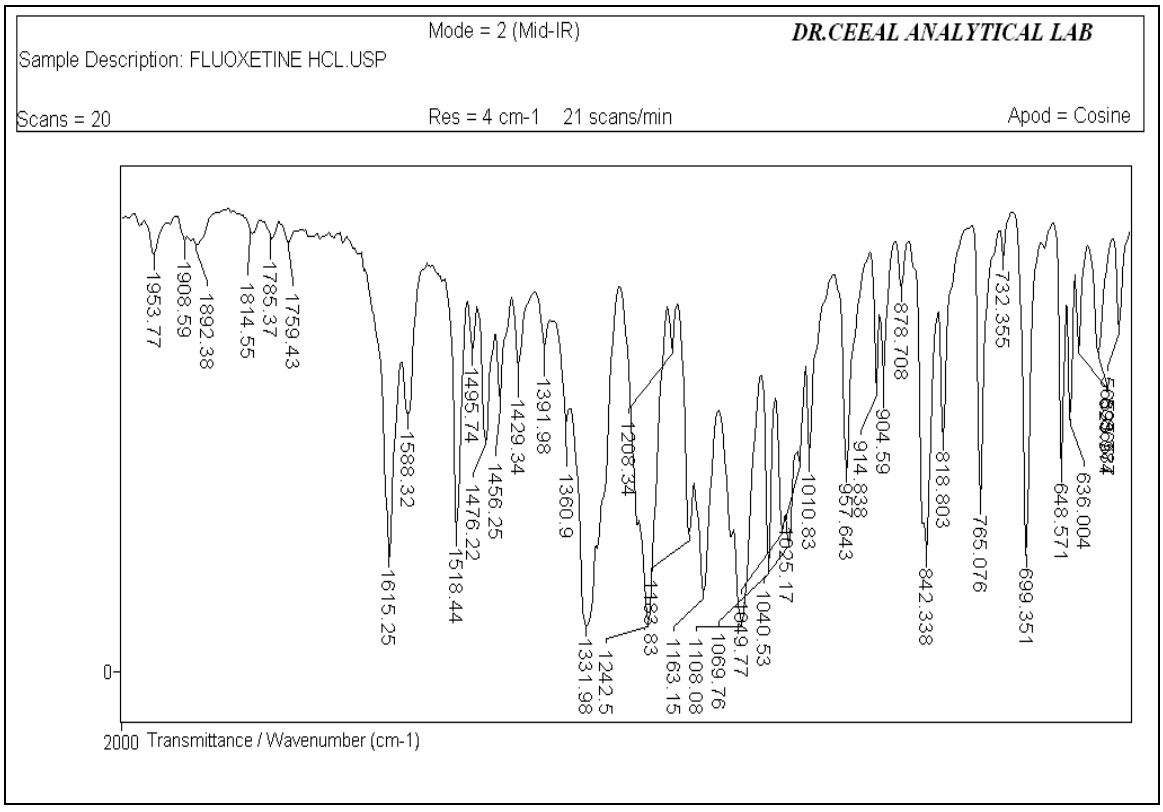


Figure 2: IR study to determine the Interaction between drug and excipients (F-7)

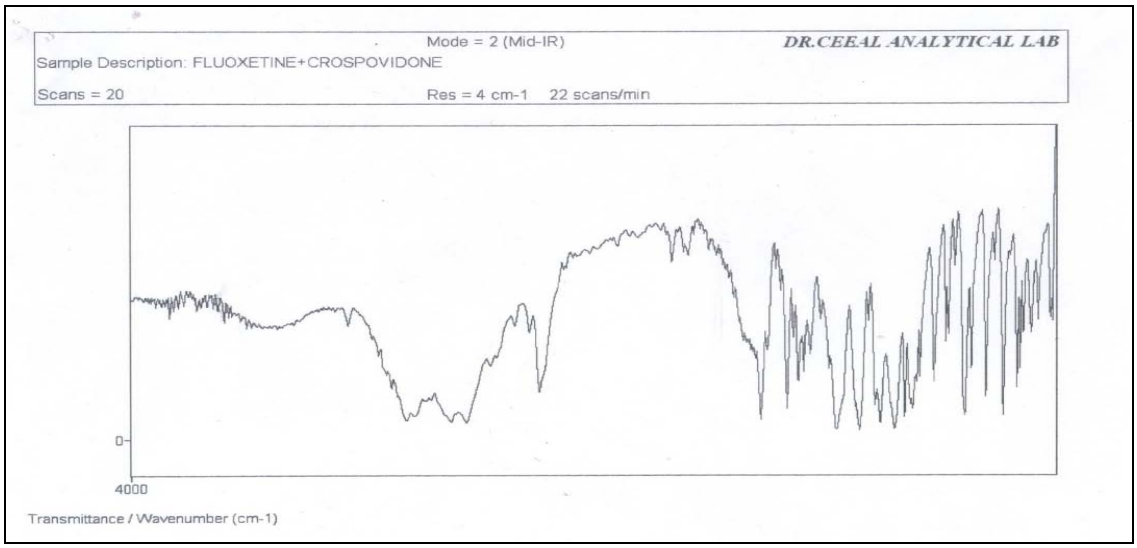


Figure 3: Differential Scanning Calorimetric Study of fluoxetine Hcl Drug

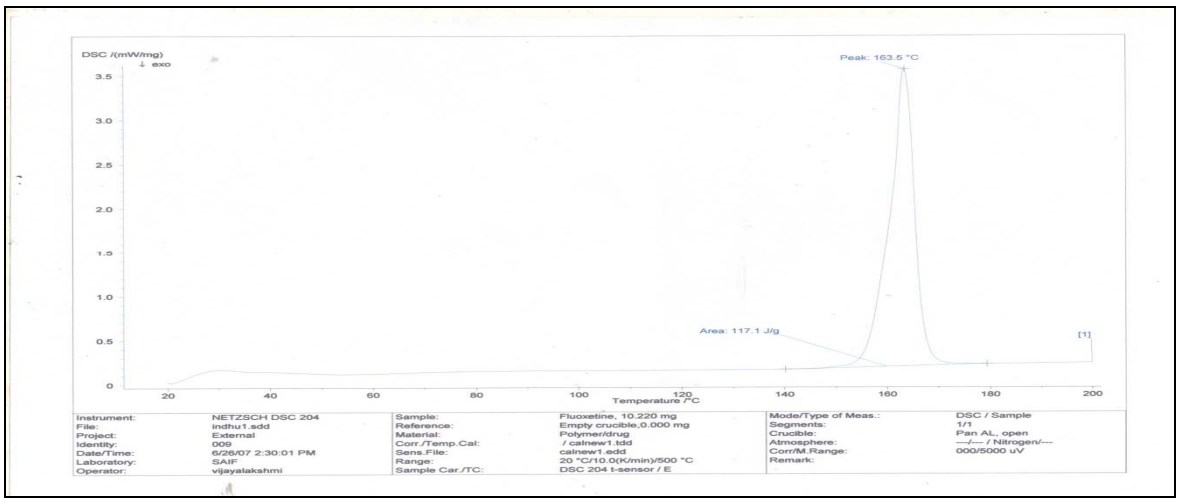


Figure 4: Differential Scanning Calorimetric Study for drug and excipients (F-7)

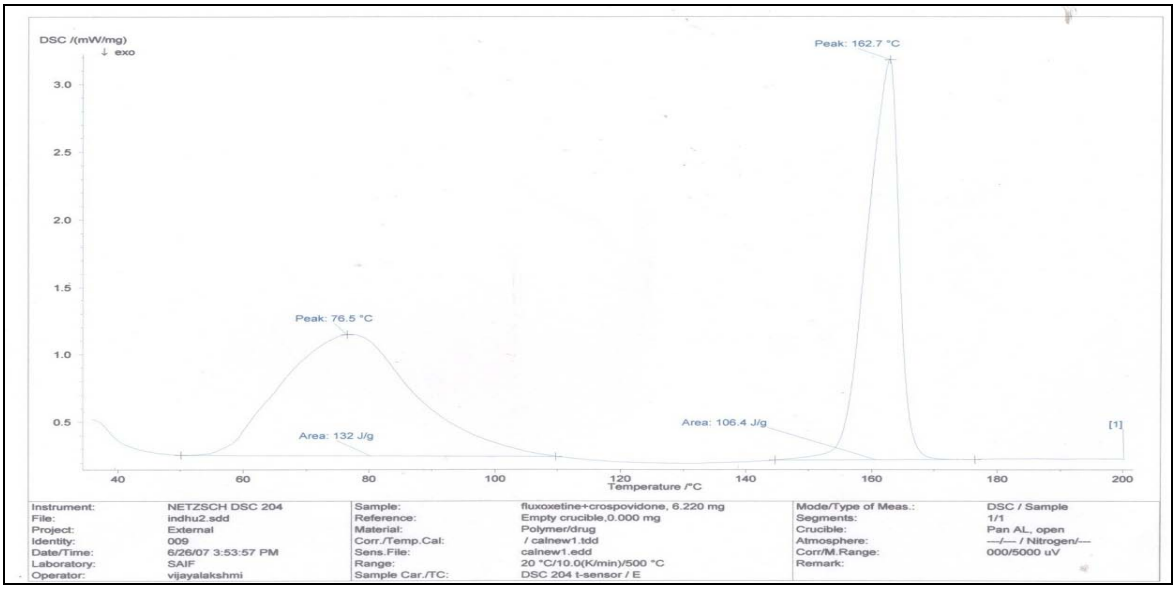


Figure 5: In-vitro dissolution profile of fluoxetine hydrochloride tablet

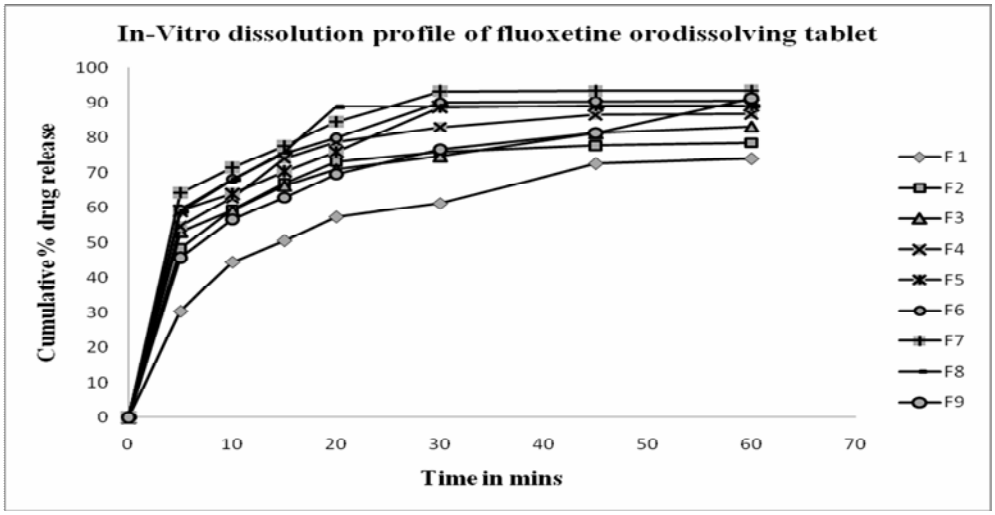


Figure 6: Zero order release kinetics graph of fluoxetine HCL orodissolving tablet (F-7)

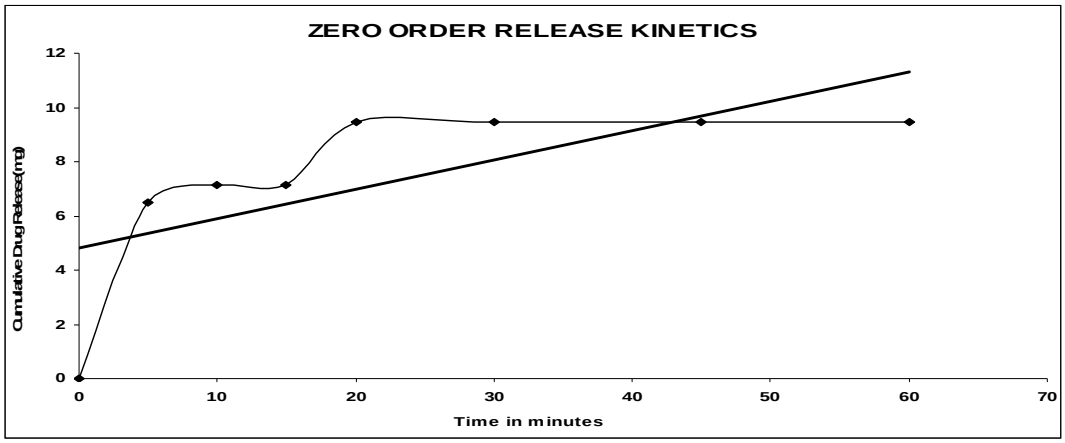


Figure 7: First order release kinetics graph of fluoxetine HCL orodissolving tablet (F-7)

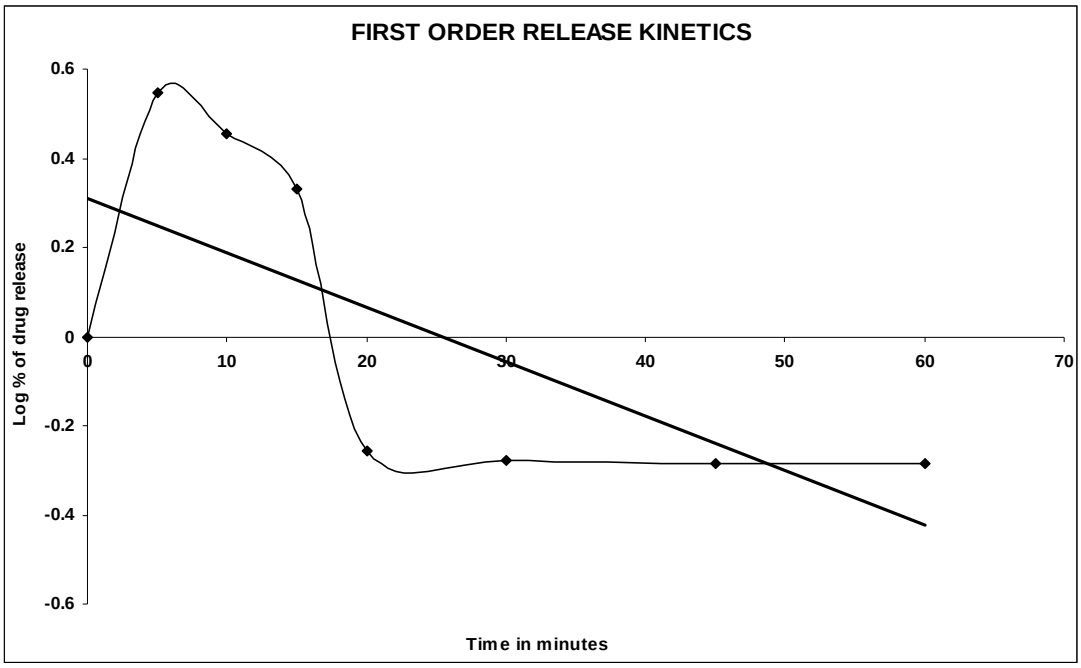
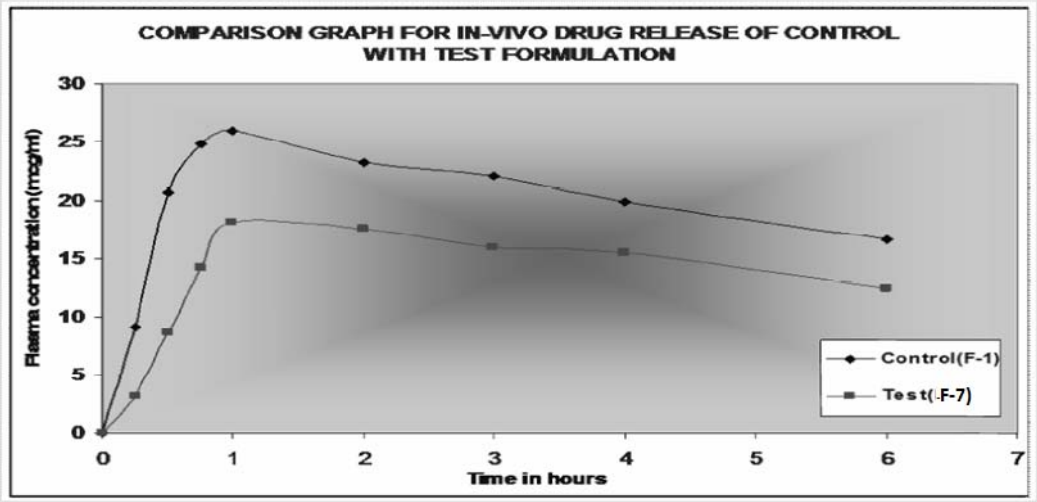


Figure 8:



The IR spectrum of fluoxetine shows us that there is no interaction between the drug and the excipient. The DSC curves observed in the case of fluoxetine shows a single sharp exothermic effect corresponding to the melting of drug was observed. **T_{peak} = 163.5º C** and ΔHt = 117.1 J/g. The DSC record of the formulation F-7 corresponds to a single exothermic peak **T_{peak} = 162.7º C** and ΔHt = 106.4 J/g and a broad exothermic peak T_{peak} = 76.5º C and ΔHt = 132 J/g due to the excipients. And the DSC thermogram shows no change in the exotherm of the pure drug of fluoxetine. From this, it was inferred that there is no interaction between the drug and excipients

The release kinetic analysis was studied for formulation F-7 for both first order and zero order kinetics. The correlation coefficient was determined and found to be -0.4214 for first order kinetics and 0.8630 for zero order kinetics. From the above data it was inferred that the dissolution profile of formulation F-7 follows zero order kinetics.

Following are the results obtained from the *in vivo* studies of both F-7 and control formulation F-I. For formulation F-7, the C_{max} was found to be 26.01µg/ml and the t_{max} is 60 mins. The AUC $_{(0-\alpha)}$ was found to be 312 µg-hr/ml. For control formulation F-I the C_{max} was found to be 17.8µg/ml and the t_{max} is 60 mins. The AUC $_{(0-\alpha)}$ was found to be 199 µg-hr/ml. The control shows a difference of percentage with that of formulation F-7. The In-vivo graph shows the increase in plasma drug concentration of test (F-7) formulation when compared to the control (F-I) formulation.

Short term accelerated stability studies were conducted for formulation F-7 and results observed reveals that there was no significant difference in the evaluated parameters namely thickness, hardness, disintegration time, percentage drug content and percentage drug release when compared with that of formulation F-7. This inference shows that the formulation should be stable.

CONCLUSION

The results have shown that Crospovidone 5% as a superdisintegrant (F-7) shows good wetting time, fastest disintegration (10 secs) and maximum drug release (97%) within 20 minutes, when compared with other formulations. This was further ascertained by the *in vivo* studies in rabbit models where formulation F-7 has shown a marked increase in drug release profile when compared to that of control and other formulations. To conclude, crospovidone at a concentration of 5% w/w is suitable for preparing fast dissolving tablet of fluoxetine.

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